Original Communication

# Boric acid and Borax Supplementation Reduces Weight Gain in Overweight Rats and Alter L-Carnitine and IGF-I Levels

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**Abstract:** The aim of this study was to investigate the effects of boric acid (BA) and borax (BX) on live weight and obesity associated molecules including leptin, L-carnitine, insulin-like growth factor 1 (IGF-I), and heat shock proteins 70 (HSP70) in rats fed with high-fat diet. A total of 60 rats were equally allocated as ND (normal diet), HF (high-fat diet), HF+BA, HF+BX, ND+BX, ND+BA. Body weight increases in HF+BA (85 g) and HF+BX (86 g) were significantly lower ($p<0.05$) compared to HF group (126 g). Boron treatment decreased serum L-carnitine level in high-fat diet (HF+BA 11.12 mg/L, HF+BX 10.51 mg/L, $p<0.05$) compared to HF group (15.57 mg/L), while no change was observed in groups ND+BA (7.55 mg/L) and ND+BX (7.57 mg/L) compared to group ND (8.29 mg/L). Neither BA nor BX supplementation in ND and HF groups altered the serum levels of HSP70 and leptin. BA and BX supplementation in rats fed HF resulted in a significant reduction in live weight. Boron compounds altered L-carnitine and IGF-1 levels in rats. These results indicate that boron compounds are beneficial in the treatment of obesity as well as in the prevention of high-fat diet-induced weight increase. Alterations in serum L-carnitine and IGF-1 levels in boron treated rats also indicate possible role of boron compounds in energy metabolism in response to high fat diet.

**Keywords:** Boron compounds, L-Carnitine, Leptin, IGF-1, HSP70, High-fat diet

## Introduction

Boron is a mineral found in nature mostly as boric acid and borax rather than in its elemental form [1]. In addition to its traditional use in the health care system, boron is widely used in industrial, agricultural, and cosmetic applications. It is rapidly absorbed and distributed throughout the body via passive diffusion after its administration [2]. Boric acid is the main form of boron species in the blood [3]. It has been reported that boron has biologically important effects such as immunostimulatory, antiosteoporotic, antiinflammatory, anticoagulants, antineoplastic and lipid lowering effects [4, 5]. Boron may alter the levels of triglycerides, glucose, urea, creatinine, steroid hormones, and the activity of various metabolic enzymes [6, 7]. The possible effect of boron on weight reduction is one of the enchanting areas because obesity has been one of the most important health problems in today's world. Hypertension, coronary heart disease, some types of cancer, gastro-intestinal disorders, rheumatism, obstructive sleep apnea and hyperlipidemia are closely related to obesity. An estimated 2.1 billion people worldwide are thought to be overweight or obese, and 2.8 million deaths are associated with obesity every year. [8, 9]. Short- and long-term weight reduction with boron supplementation have been shown [10, 11] although the mechanism of its action seems to be complex. Aysan et al. has showed that boric acid might have a weight reducing effect by increasing the catabolism of lipids and glucose [10]; however, the effects of boron supplementation on obesity and energy homeostasis largely unknown. In this study, we investigated the effects of boron on serum levels of leptin, L-carnitine, heat shock proteins 70 (HSP70), and insulin-like growth factor 1 (IGF-I) which have been associated with energy metabolism and obesity.

Leptin is an important hormone for energy homeostasis and considered a marker for obesity [12]. It is synthesized from adipose tissue, which regulates lipid metabolism by stimulating lipolysis and inhibiting lipogenesis [13]. Obese individuals generally exhibit higher blood leptin hormone levels relative to normal individuals because obese people show reduced sensitivity for this hormone [14]. Another important molecule in fatty acid metabolism and energy production is L-carnitine [15]. L-carnitine is a cofactor which serves in the transfer of long chain fatty acids into the mitochondria, in the β-oxidation of fatty acids and in the storage of energy [16]. L-carnitine deficiency occurs in aberrations of its regulation and can be frequently seen in obesity [17]. Most of the lipids cannot be used as energy sources in the event of L-carnitine deficiency in the body, and fatty acid accumulation leads to obesity. Recently, it has been reported that L-carnitine supplementation could reduce high-fat diet-induced obesity [18, 19]. IGFs have similar metabolic effects as insulin in the body. By inhibiting proteolysis in skeletal muscle tissue, it plays a role in mediation of protein synthesis and metabolic activity of growth hormone [20, 21].

While obesity-induced inflammation depends on various classical inflammatory mediators, the stress response is more complex and includes an impairment of the Heat Shock Response (HSR) [22, 23]. This HSR involves a set of highly conserved proteins called Heat Shock Proteins (HSPs), which are also known as molecular chaperones or Glucose Regulated Proteins (GRPs), and are essential for protection and recovery from tissue damage [22, 23]. HSP72 was shown to protect against obesity-induced insulin resistance [24, 25].

In this study, long term effects of boron as in the form of boric acid (BA) and borax (BX) on body weight and weight reducing ability, as well as the levels of leptin, L-carnitine, IGF-I and HSP70 were investigated in rats fed with a high-fat diet in comparison with the rats fed with normal diet for 8 weeks. In addition, the differential effect of different boron compounds (BA and BX) on live weight increase and the other parameters was evaluated in this study.

## Materials and Methods

### Experimental Protocol

In this study, 60 Sprague Dawley male rats with the average weight of 218.34 ± 10.39 g at 2–3 months of age were purchased from The Animal Breeding Laboratories of The Experimental Research and Application Center (Elazığ, Turkey). Before the experimental procedure, the permission for the use of laboratory animals was obtained from Kafkas University Animal Experimentation Ethics Board (KAU-HADYEK: 2012-67, Turkey). Animals were kept at room temperature (25°C) and relative humidity (50-55%) in a 12- hour light and dark cycle.

Animals were fed a normal pelleted diet (Bayramoğlu-Erzurum, Turkey), and drinking water was provided *ad libitum*. Standard feeding and high-fat diet calorie composition used during the 8-week experimental period are shown in Table I. Animals were divided into 6 groups each containing 10 rats as follows: Group ND (control; normal food and drinking water), Group HF (high-fat diet and drinking water), Group HF+BA received a high-fat diet and boric acid (BA) (5.72 mg/L $H_3BO_3$ (Sigma, St. Louis, MO, USA) dissolved in distilled water) containing 1 mg/L boron in drinking water according to previously reported method [10]. Group HF+BX was treated with a high-fat diet and borax (8.82 mg/L $Na_2B_4O_7{\cdot}10H_2O$ (Sigma) dissolved in distilled water) containing a final concentration of 1 mg/L of boron in drinking water. Group ND+BX was fed with a normal diet (ND) and borax (8.82 mg/L $Na_2B_4O_7{\cdot}10H_2O$ in drinking water) containing a final concentration of 1 mg/L of boron. Group ND+BA was fed with a normal diet and boric acid (5.72 mg/L $H_3BO_3$ in drinking water) containing a final concentration of 1 mg/L of boron. Final boron concentration was determined from previously published reports [10, 11].

## Blood samples Collection

Animals were anesthetized using combination of intraperitoneal 10 mg/kg xylazine and 60 mg/kg ketamine (60 mg/kg) at the end of experiment. Blood samples of animals were collected into the serum tubes via cardiac puncture. Samples were then centrifuged at 3500 rpm for 10 minutes at +4°C and the serum samples were obtained. The samples were kept at −20°C until analyses.

## Determination of leptin, HSP70 and IGF-I levels in serum

Leptin (Hangzhou East Biopharm, Torrance, USA), HSP70 (Enzo Life Sciences GmbH, Lorrach, Germany) and IGF-I levels (Mediagnost GmbH, Germany) were determined using ELISA kits with a spectrophotometer (EoBiotex, USA) according to the provided instructions by the suppliers.

## Determination of L-carnitine levels in serum

Serum L-carnitine levels were measured according to a previous report [26]. The method is based on the reaction

 

**Table I.** Content and calorie values of normal and high-fat diet used in the experiment

| Ingredients | (%) | Composition and calorie values of the experimental diets | | |
|---|---|---|---|---|
| Corn | 60.50 | Contents of Nutrients | Normal | High-fat |
| Gluten Meal | 33.45 | Dry matter (%) | 89.60 | 83.80 |
| Vegetable fat | 3.30 | Crude protein (%) | 23.90 | 24.30 |
| Marble dust | 1.0 | Crude fat (%) | 20.63 | 53.83 |
| Dicalcium phosphate | 0.5 | Crude cellulose (%) | 7.17 | 7.12 |
| Sodium chloride | 0.5 | Crude ash (%) | 8.43 | 8.37 |
| DL-Methionine | 0.10 | Calorie (ME: kcal.kg$^{-1}$) | 2600 | 5616 |
| Lysine | 0.15 | | | |
| Vitamin-mineral premix[a] | 0.5 | | | |

[a]Mix supplied per 1.0 kg: 20,000,000 IU Vitamin A, 3000,000 IU Vitamin D3, 25 g Vitamin E, 4 g Vitamin B1, 8 g Vitamin B2, 5 g Vitamin B6, 20 mg Vitamin B12, 20 g nicotinamide, 12 g calcium-o-pantothenic acid, 200 g choline chloride, 50 g manganese, 50 g iron, 50 g zinc, 10 g copper, 0.8 g iodine, 0.15 g cobalt, 0.15 g selenium. (ME): Metabolizable energy (kcal.kg$^{-1}$)

catalyzed by the carnitine acetyltransferase (CAT) (EC. 2.3.1.7) acting on L-carnitine. Acyl group of acyl-CoA is transferred to carnitine by the CAT. Free coenzyme A reacts with 5,5-dithiobis (2-nitrobenzoic acid), forming phenolate ion, and its formation is proportional to the amount of L-carnitine and measured by a spectrophotometer at 405 nm.

## Statistical Analyses

Data obtained from the study were expressed as mean ± SEM and initially analyzed for normality by Kolmogorov Smirnov test (found as $p>0.05$). Then the data were analyzed by one-way analysis of variance (ANOVA), followed by Tukey post-hoc tests using SPSS software computer program. P values smaller than 0.05 were considered significant.

## Results

### Effect on Leptin, HSP70, L-carnitine and IGF-I

Changes in leptin, HSP70, L-carnitine, and IGF-I levels in the groups are shown in Table II. Leptin levels were significantly increased in the high-fat diet group (HF) compared to normal diet (ND). Although leptin levels in HF+BA and HF+BX groups were not significantly lower than those of high fat only group, these values were not different from those of control group (ND). Similarly, leptin levels in groups ND+BA and ND+BX were not different from ND group. In terms of the differential effect of Boric acid and Borax on leptin level, no difference was observed between HF+BA and HF+BX groups as well as ND+BA and ND+BX.

Serum free carnitine levels were significantly increased in high-fat diet group compared to normal diet group. Serum carnitine levels in boron supplemented high fat groups (HF+BA and HF+BX) were lower than in high fat group, but these values were similar to those of control. On the other hand, serum carnitine levels in groups ND +BA and ND+BX were not different from group receiving normal diet only (group ND). Serum carnitine levels in groups of HF+BA and HF+BX have higher serum carnitine levels compared to groups ND+BA and ND+BX.

IGF-I levels in high-fat diet group (HF) significantly lower than in normal diet (ND). IGF-I level in group HF+BX were significantly lower than those of both normal (ND) and high-fat diet (HF) groups, whereas IGF-I level in group HF +BA was not different from group HF. IGF-I levels in ND +BA and ND+BX groups were significantly decreased compared to ND group. The decrease in IGF-I level of group ND +BX was greater than that of group ND+BA.

HSP70 levels were not changed in any of the tested groups in this study.

## Effect on live weight of rats

Live weights of all animals were monitored weekly for 8 weeks. Live body weights before and after the experiment as well as weight increases in groups were presented in Figure 1. The increase in live weight of animals fed with the high-fat diet (HF) was higher compared to the normal diet (ND) group. The groups treated with boric acid and borax compounds in high fat diet (HF+BA and HF+BX) were found to have lower body weight increases at the end of the experiment compared to the group in high fat diet only (HF) (Figure 1). There was no difference in body weight increases between group HF+BA and group HF+BX. While the body weight increase in group treated with boric acid

**Table II.** The Effect of boric acid and borax on serum levels of leptin, HSP70, L-carnitine and IGF-I levels in rats (n=10 for each group) fed normal or high-fat diets.

| Parameters | ND n=10 | HF n=10 | ND+BA n=10 | HF+BA n=10 | ND+BX n=10 | HF+BX n=10 | P |
|---|---|---|---|---|---|---|---|
| Leptin (ng/ml) | 3.09±0.09$^{b}$ | 3.52±0.133$^{a}$ | 3.13±0.067$^{b}$ | 3.34±0.091$^{ab}$ | 3.29±0.054$^{ab}$ | 3.33±0.078$^{ab}$ | P<0.05 |
| HSP70 (ng/ml) | 0.179±0.060 | 0.169±0.049 | 0.115±0.003 | 0.195±0.107 | 0.210±0.058 | 0.114±0.029 | Ns |
| L-Carnitine (mg/L) | 8.29±0.84$^{bc}$ | 15.57±0.92$^{a}$ | 7.55±0.44$^{c}$ | 11.12±1.54$^{b}$ | 7.57±0.69$^{c}$ | 10.51±1.42$^{b}$ | P<0.001 |
| IGF-I (ng/ml) | 582.15±17.36$^{a}$ | 537.23±11.70$^{b}$ | 469.76±15.51$^{c}$ | 547.12±9.33$^{ab}$ | 412.61±12.05$^{d}$ | 489.93±12.45$^{c}$ | P<0.001 |

Group values are presented as mean**±SEM**. Different superscript letters (a, b, c) within the same row indicate significant differences. Not significant (**Ns**), normal diet (**ND**), high-fat diet (**HF**), boric acid (**BA**) and borax (**BX**), Heat Shock Protein 70 **(HSP70)**, Insulin-like growth factor 1 **(IGF-I)**, n=10 for each group.

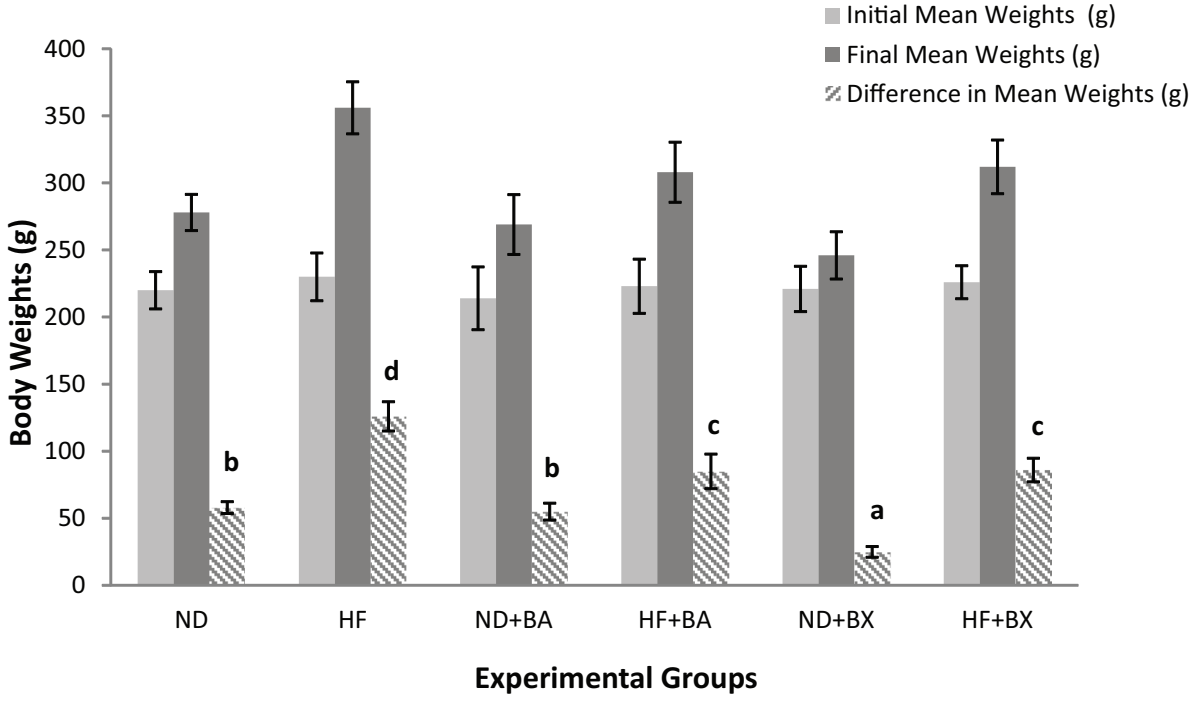


**Figure 1.** Effects of Borax and Boric acid on body weight increase in experimental groups, n=10 for each group.

and normal diet (ND+BA) was not different from the group receiving normal diet only (ND), the increase in body weight of group ND+BX was reduced compared to group ND.

## Discussion

In this study, it is aimed to investigate whether boron has an effect on serum levels of leptin, L-carnitine, IGF-I and HSP70 which are known to be associated with energy metabolism. It was found in the present study that leptin levels were significantly increased in the high-fat diet compared to normal diet. Our findings were in agreement with other studies which demonstrated that high-fat diet increased leptin levels [27, 28]. In a study conducted by Nascimento et al. rats which were fed with normal (12% fat) and high-fat (49% fat) diets for 15 to 45 weeks significantly increased live weight and leptin levels of the rats at the end of the treatment [27]. Their findings were subsequently corroborated in another study where a significant increase in live weight and plasma leptin levels in rats were measured after the rats were fed a 30% fat diet in addition to normal rations for 10 weeks [28]. It is reported that the increase in leptin levels in blood circulation is closely related to the increase in adipose tissue [29]. Hence, increased leptin level in high-fat group compared to normal diet might be due to increased fat in the body of animals.

In the present study, although leptin levels in HF+BA and HF+BX groups were not significantly lower than those of high fat only group, these values were not different from those of control group (ND). Similarly, boron supplementation in normal diet groups did not affect leptin levels

 

compared to the group fed with normal diet. Cheng et al. (2011) reported that ostrich chicks treated with boron in drinking water showed significantly higher leptin levels when compared to the control group [30]. Küçükkurt et al. (2015) has reported that boron supplementation for 4 weeks caused a decrease in serum leptin levels in rats [11]. This result could be explained by the fact that boron might have normalized the signals to appetite centers in the brain that were desensitized towards leptin [11]. Differences among the reports could be related to the variations in the duration of boron exposure and the amounts of boron used or alterations in the physiology of different animals.

L-carnitine levels in serum samples of the rats (group HF) fed with high-fat diet for 8 weeks were significantly higher than that of group ND. These findings were consistent with the results of previous studies indicating that high-fat diet increased the L-carnitine levels [15, 31]. Changes in L-carnitine metabolism were reported in different pathological conditions including diabetes mellitus, malignancies, myocardial ischemia, and alcohol abuse. In addition, elimination can also be influenced by different factors including thyroid hormones, adrenocorticotrophin (ACTH) and diet, all could also influence urinary excretion of L-carnitine [32]. Serum carnitine levels in boron supplemented high fat groups (HF+BA and HF+BX) were lower than in high fat group only, but these values were similar to those of control. On the other hand, serum carnitine levels in groups of HF+BA and HF+BX are higher than in groups ND+BA and ND+BX. Similarly, serum free carnitine levels in groups ND+BA and ND+BX were not different from control group's values. Moreover, there was no differential effect of both BX and BA on L-carnitine levels. In a different study, boron added to the diet in 100 mg/kg for 4 weeks increased serum L-carnitine level in rats [11]. L-carnitine plays a crucial role in fat metabolism by transporting long-chain fatty acids for production of energy via β-oxidation and oxidative phosphorylation. It also facilitates the removal of short- and medium-chain fatty acids accumulated as a result of fat metabolism from mitochondria [33]. By playing these critical roles, L-carnitine regulates fat and carbohydrate metabolism. Increasing L-carnitine in muscle tissue increases fat oxidation and glycogen storage, but decreases muscle glycolysis [26]. Wall et al (2011) demonstrated that increasing L-carnitine in muscle tissue via oral carnitine supplementation along with carbohydrate feeding reduces body mass compared to control group treated with carbohydrate feeding only [34]. Carnitine is taken up by muscle tissue from the bloodstream, and is stored mainly in muscle [32]. It can be speculated that boron may increase the mobilization of carnitine to muscle tissue from the bloodstream to be used up for fatty acid oxidation.

In this study, it was found that IGF-I levels in group ND were significantly lower than the group fed a high-fat diet. IGF-I level in group HF+BX were significantly lower than that of high-fat diet (HF) group, whereas IGF-I level in group HF+BA was not different from group HF. IGF-I levels in ND+BA and ND+BX groups were significantly decreased compared to ND group. The decrease in IGF-I level of group ND+BX was greater than that of group ND+BA. IGF-I level in group HF+BX were significantly lower than those of both normal (ND) and high-fat diet (HF) groups, whereas IGF-I level in group HF+BA was not different from group HF. IGF-I levels in ND+BA and ND+BX groups were significantly decreased compared to ND group. The decrease in IGF-I level of group ND+BX was greater than that of group ND+BA. Generally, the effects of the growth hormone on tissues are regulated by IGF-I. Previous reports argued that IGF-I levels did not change in obese individuals [35, 36]; however, some studies reported a decrease [37, 38] and some reported an increase in IGF-I levels [39]. Generally, the effects of the growth hormone on tissues are regulated by IGF-I. Growth hormone (GH) and IGF-I exert their effects in multiple mechanisms. GH has a reducing effect on visceral fat, and GH reduces lipogenesis in the hepatocytes. IGF-I improves insulin resistance and mitochondrial function, on the other hand decreases reactive oxygen species and triglyceride accumulation in the hepatocytes. [40]. In the current study, except for BA in group HF+BA, boron compounds decreased the IGF-I levels in both HF and ND groups. This reducing effect of boron compounds on IGF-I level is unexpected considering the role of IGF-I on fat metabolism.

HSP70, synthesized during stress, binds on the hydrophobic residues of proteins and prevents their possible denaturation and aggregations. It is responsible for protecting the cells from the temperature and oxidative damage [41, 42]. It has been reported that heat shock response is disturbed in obese individuals [24, 25]. It has also been reported that HSP70 levels increased as a result of high-fat-induced glucose and insulin intolerance. The increase in HSP70 levels could be related to the increase in insulin sensitivity and the regulation of the glucose tolerance [43]. Ghayour-Mobarhan et al. (2007) have reported that the HSP70 levels in obese individuals were significantly higher than the individuals who had normal weight or overweight [44]. However, in our study, no significant difference was found in HSP70 levels between the high-fat group and the ND group. In addition, there were no statistically significant differences in HSP70 levels between the groups that were administered boron compounds. While obesity-induced inflammation depends on various classical inflammatory mediators, the stress response is more complex and includes an impairment of the Heat Shock Response (HSR) [22, 23]. Lack of alteration in HSR level in this study could indicate that the treatment may not induce enough stress response in the rats.

Secondly, we aimed to investigate if boron has a weight reducing effect on rats which were fed with high-fat diet. As expected, high-fat diet resulted in significant weight increase in HF group compared to normal diet at the end of 8 weeks. Boron in either borax or boric acid forms added to drinking water significantly decreased the live weight of rats treated with high-fat diet (HF+BA and HF+BX). Moreover, there was no difference in body changes between group HF+BA and group HF+BX indicating that borax and/or boric acid have no differential effect on body weight reducing effect in high fat treatment. Boron plays a role in energy substrate metabolism by influencing hepatic glycolytic concentrations and lipid metabolism especially on serum triglycerides and VLDL secretion of the liver [45]. The role of boron on energy metabolism is reported to be involved in its ability to decrease fat infiltration in the liver and to reduce visceral fat amount [46]. In the present study, while the body weight increase in group treated with boric acid and normal diet (ND+BA) was not different from the group receiving normal diet only (ND), the increase in body weight of group ND+BX was reduced compared to group ND. Boric acid did not change the body weights in normal diet, but borax reduced the body weights compared to normal diet only. Contrary to our results, Aysan et al (2011) reported that boron as in boric acid form reduced the body weight significantly in mice which were fed with normal diet [10]. In another study investigating the weight reducing effect of boric acid, Aysan et al., (2013) reported similar results indicating weight reducing effect of boric acid in mice [47]. The weight reducing effect was reported to be associated with increased expression of mitochondrial uncoupling proteins in adipose tissues and muscle tissue indicating increased metabolic rate in boric acid treated mice. Because boron supplementation causes high protein synthesis, weight gain might be due to muscle mass [46, 45].

BA and BX supplementation in rats fed with HF resulted in significant reductions in live weight. This study guided the dosing strategy of boron compounds in either BA or BX forms in the treatment of obesity and its associated diseases and allowed the simulation of long-term clinical outcomes on weight increase and obesity related several important molecules. In addition, findings of this study indicated possible involvement of boron compounds on L-carnitine and IGF-1 which both play important roles in fatty acid metabolism and mitochondrial functions in energy metabolism. However, the molecular mechanism of alterations in L-carnitine and IGF-1 levels in response to boron treatments and the detailed molecular effects of these alterations to the fat and protein metabolism in obesity and during high fat diet remain to be determined in the mechanistic level. Additional studies are needed to reveal the molecular mechanism and interaction with other biomolecules of boron in order to be used potentially in the treatment of obesity and obesity-related diseases.

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**Conflict of Interest**
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